Answer 1:

Bibliographic Information

In vivo and Microarray Analysis of Rexinoid-Responsive Anaplastic Thyroid Carcinoma.   Klopper, Joshua P.; Berenz, Andrew; Hays, William R.; Sharma, Vibha; Pugazhenthi, Umarani; Janssen, Jennifer; Singh, Meenakshi; Bissonnette, Reid P.; Haugen, Bryan R.   Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes,   University of Colorado at Denver and Health Sciences Center,   Aurora,   CO,   USA.   Clinical Cancer Research   (2008),   14(2),   589-596. Publisher: American Association for Cancer Research,   CODEN: CCREF4   ISSN: 1078-0432.   Journal   written in English.   AN 2008:106243   CAPLUS   (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: Anaplastic thyroid carcinoma is rare, yet lethal despite aggressive therapy. Mol. targeting may be beneficial using the rexinoid LGD1069, a retinoid X receptor-selective agonist, as a novel treatment. In this report, we describe the efficacy of LGD1069 in anaplastic thyroid carcinoma in vitro and assess the in vivo treatment effects on a responsive cancer. Addnl., we explore potential mediators of the rexinoid effect on a responsive anaplastic thyroid cancer using comparative microarray anal. Exptl. Design: Anaplastic thyroid cancer cell lines DRO, ARO, and FRO were treated with LGD1069 in vitro. Responsive DRO xenograft tumors were treated with control chow or chow contg. a low dose (30 mg/kg/d) or a high dose (100 mg/kg/d) of LGD1069. Comparative microarray anal. of DRO cells treated with LGD1069 compared with vol.-equiv. control was assessed after 24 h of treatment to evaluate early gene expression changes. RESULTS: DRO xenograft tumor growth was inhibited by LGD1069 treatment in a dose-dependent manner. Comparative microarray anal. showed that 80 genes had a significant increase in expression and 29 genes had a decrease in expression after 24 h of treatment with LGD1069. Expression of angiopoietin-like 4 (ANGPTL4) mRNA was increased 6.5-fold. A trend towards an increase in ANGPTL4 mRNA (not statistically significant) was seen in treated tumors in vivo and this correlated with decreased tumor vascularity and increased necrosis. CONCLUSIONS: LGD1069 therapy decreases proliferation in an anaplastic thyroid cancer cell line that expresses retinoid X receptor-γ, and this effect is confirmed with decreased tumor size in vivo in a nude mouse model. ANGPTL4 is increased in DRO in response to LGD1069 and may be a potential mediator of the effects of rexinoid treatment.

Answer 2:

Bibliographic Information

A selective retinoid X receptor agonist bexarotene (LGD1069, targetin) inhibits angiogenesis and metastasis in solid tumours.   Yen, W-C.; Prudente, R. Y.; Corpuz, M. R.; Negro-Vilar, A.; Lamph, W. W.   Department of Molecular Oncology,   Ligand Pharmaceuticals, Inc.,   San Diego,   CA,   USA.   British Journal of Cancer   (2006),   94(5),   654-660. Publisher: Nature Publishing Group,   CODEN: BJCAAI   ISSN: 0007-0920.   Journal   written in English.   CAN 145:224399   AN 2006:208047   CAPLUS   (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The present study detd. the influence of a retinoid X receptor agonist bexarotene on angiogenesis and metastasis in solid tumors. In the exptl. lung metastasis xenograft models, treatment with bexarotene inhibited the development of the lung tumor nodule formation compared to control. In vivo angiogenesis assay utilizing gelfoam sponges, bexarotene reduced angiogenesis in sponges contg. vascular endothelial growth factor, epidermal growth factor and basic fibroblast growth factor to various extent. To det. the basis of these observations, human breast and non-small-cell lung cancer cells were subjected to migration and invasion assays in the presence of bexarotene. Our data showed that bexarotene decrease migration and invasiveness of tumor cells in a dose-dependent manner. Furthermore, bexarotene inhibited angiogenesis by directly inhibiting human umbilical vein endothelial cell growth and indirectly inhibiting tumor cell-mediated migration of human umbilical vein endothelial cells through Matrigel matrix. Anal. of tumor-conditioned medium indicated that bexarotene decreased the secretion of angiogenic factors and matrix metalloproteinases and increased the tissue inhibitor of matrix metalloproteinases. The ability of bexarotene to inhibit angiogenesis and metastasis was dependent on activation of its heterodimerization partner peroxisome proliferator-activated receptor γ. Collectively, our results suggest a role of bexarotene in treatment of angiogenesis and metastasis in solid tumors.

Answer 3:

Bibliographic Information

A selective fetinoid X receptor agonist bexarotene (targretin) prevents and overcomes acquired paclitaxel (taxol) resistance in human non-small cell lung cancer.   Yen, Wan-Ching; Corpuz, Manny R.; Prudente, Rene Y.; Cooke, Tracy A.; Bissonnette, Reid P.; Negro-Vilar, Andres; Lamph, William W.   Department of Molecular Oncology, Ligand Pharmaceuticals, Inc., San Diego, CA, USA.   Clinical Cancer Research (2004), 10(24), 8656-8664. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English.   CAN 142:329067   AN 2004:1150205   CAPLUS   (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Paclitaxel is an important anticancer agent for the treatment of non-small cell lung cancer (NSCLC). However, its use in cancer therapy is limited by development of acquired drug resistance. The goal of this study was to det. the effect of bexarotene on development of acquired paclitaxel resistance in NSCLC. Human NSCLC Calu3 cells were repeatedly treated in culture with intermittent paclitaxel alone or in combination with continuous bexarotene for 3 mo. Thereafter, cells were isolated and characterized for their drug sensitivity in vitro and in vivo. Repeat exposure to paclitaxel alone resulted in development of paclitaxel resistance with cross-resistance to multidrug resistance P-glycoprotein substrates, whereas the bexarotene/paclitaxel combination prevented the development of drug resistance and the cells remained chemosensitive. Furthermore, paclitaxel resistance could be overcome when the resistant cells were treated with the combination regimen. Fluctuation anal. showed that treatment with bexarotene decreased the rate of spontaneous development of paclitaxel resistance. In vivo, the bexarotene/paclitaxel combination regimen produced a statistically significant decrease in tumor growth in a Calu3 NSCLC xenograft model compared with the single agents (two-tailed, $P < 0.05$). In addn., paclitaxel-resistant Calu3 tumors treated with the bexarotene/paclitaxel combination showed greater delay in tumor growth compared with those treated with paclitaxel alone. Our results suggest that bexarotene may offer a novel approach to prevent and overcome paclitaxel resistance in patients with NSCLC.

Answer 4:

Bibliographic Information

Bexarotene (LGD1069, Targretin), a selective retinoid X receptor agonist, prevents and reverses gemcitabine resistance in NSCLC cells by modulating gene amplification.   Tooker Patricia; Yen Wan-Ching; Ng Shi-Chung; Negro-Vilar Andres; Hermann Thomas W   Department of Molecular Oncology, Ligand Pharmaceuticals, Inc., San Diego, California 92121, USA   Cancer research (2007), 67(9), 4425-33. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE) written in English.   PubMed ID 17483357 AN 2007273525   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Acquired drug resistance is a major obstacle in cancer therapy. As for many other drugs, this is also the case for gemcitabine, a nucleoside analogue with activity against non-small cell lung cancer (NSCLC). Here, we evaluate the ability of bexarotene to modulate the acquisition and maintenance of gemcitabine resistance in Calu3 NSCLC models. In the prevention model, Calu3 cells treated repeatedly with gemcitabine alone gradually developed resistance. However, with inclusion of bexarotene, the cells remained chemosensitive. RNA analysis showed a strong increase of rrm1 (ribonucleotide reductase M1) expression in the resistant cells (Calu3-GemR), a gene known to be involved in gemcitabine resistance. In addition, the expression of genes surrounding the chromosomal location of rrm1 was increased, suggesting that resistance was due to gene amplification at the chr11 p15.5 locus. Analysis of genomic DNA confirmed that the rrm1 gene copy number was increased over 10-fold. Correspondingly, fluorescence in situ hybridization analysis of metaphase chromosomes showed an intrachromosomal amplification of the rrm1 locus. In the therapeutic model, bexarotene gradually resensitized Calu3-GemR cells to gemcitabine, reaching parental drug sensitivity after 10 treatment cycles. This was associated with a loss in rrm1 amplification. Corresponding with the in vitro data, xenograft tumors generated from the resistant cells did not respond to gemcitabine but were growth inhibited when bexarotene was added to

the cytotoxic agent. The data indicate that bexarotene can resensitize gemcitabine-resistant tumor cells by reversing gene amplification. This suggests that bexarotene may have clinical utility in cancers where drug resistance by gene amplification is a major obstacle to successful therapy.

Answer 5:

Bibliographic Information

The retinoid X receptor-selective ligand, LGD1069, inhibits tumor-induced angiogenesis via suppression of VEGF in human non-small cell lung cancer.   Fu Jianjiang; Ding Yan; Huang Dan; Li Hongyan; Chen Xiaoguang Department of Pharmacology, Institute of Materia Medica, Chinese Academy of Medical Sciences and Peking Union Medical College, 1 Xian Nong Tan Street, Beijing 100050, China   Cancer letters (2007), 248(1), 153-63. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE) written in English.   PubMed ID 17027148 AN 2007133405   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The present study determined the influence of a retinoid X receptor agonist LGD1069 on angiogenesis in non-small cell lung cancer. In A549 xenograft models, treatment with LGD1069 inhibited the growth and CD31 expression compared with control. In vivo angiogenesis assay utilizing hollow fiber, LGD1069 reduced density of capillary network induced by tumor cells. To determine the basis of these observations, we examined the expression of VEGF and activation of JNK and ERK in A549 cells exposed to LGD1069. Our data showed that LGD1069 decrease the VEGF expression of tumor cells in a dose-dependent manner. Furthermore, it was demonstrated that the decreasing expression of VEGF was consist with inhibition of JNK and ERK activation induced by LGD1069. Collectively, our results suggest a role of LGD1069 in treatment for non-small cell lung cancer by inhibition of tumor-induced angiogenesis.

Answer 6:

Bibliographic Information

Identification of biomarkers modulated by the rexinoid LGD1069 (bexarotene) in human breast cells using oligonucleotide arrays.   Kim Hee-Tae; Kong Gu; Denardo David; Li Yuxin; Uray Ivan; Pal Sunita; Mohsin Syed; Hilsenbeck Susan G; Bissonnette Reid; Lamph William W; Johnson Karen; Brown Powel H   Breast Center, Baylor College of Medicine, Houston, Texas 77030, USA   Cancer research (2006), 66(24), 12009-18. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) written in English.   PubMed ID 17178900 AN 2006739957   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Retinoids have been found to be promising chemopreventive agents that play an important role in regulating cell growth, differentiation, and apoptosis. The action of retinoids is mediated by retinoid receptors (retinoic acid receptors and retinoid X receptors), which are nuclear transcription factors that, when bound to retinoids, regulate gene expression. LGD1069 is a highly selective RXR agonist that has reduced toxicity compared with retinoids. Our previous studies have shown that RXR-selective ligands (or "rexinoids"), including LGD1069, can inhibit the growth of normal and malignant breast cells and can suppress the development of breast cancer in transgenic mice. For the current study, we attempted to identify biomarkers of the chemopreventive effect of the RXR-selective retinoid LGD1069. In these experiments, we used Affymetrix microarrays to identify target genes that were modulated by LGD1069 in normal human breast cells. Affymetrix and dChip analysis identified more than 100 genes that were up-regulated or down-regulated by LGD1069 treatment. We then tested 16 of these genes in validation experiments using quantitative reverse transcription-PCR and Western blotting of independently prepared samples, and found that 15 of 16 genes were modulated in a similar manner in these validation experiments as in the microarray experiments. Genes found to be regulated include known

retinoid-regulated genes, growth regulatory genes, transcription factors, and differentiation markers. We then showed that the expression of several of these rexinoid-regulated biomarkers is modulated in vivo in mammary glands from mice treated with LGD1069. These critical growth-regulating proteins will be promising targets of future agents for the prevention and treatment of breast cancer.

Answer 7:

Bibliographic Information

Differentiation and growth inhibition mediated via the RXR:PPARgamma heterodimer in colon cancer.   Cesario Rosemary M; Stone Jessica; Yen Wan-Ching; Bissonnette Reid P; Lamph William W   Department of Molecular Oncology, Ligand Pharmaceuticals, San Diego, CA 92121, USA. rcesario@ligand.com   Cancer letters (2006), 240(2), 225-33. Journal code: 7600053. ISSN:0304-3835. Journal; Article; (JOURNAL ARTICLE) written in English.   PubMed ID 16271436 AN 2006452338   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

This study evaluated the anti-tumor efficacy of combining the RXR agonist, bexarotene, with the PPARgamma agonist, rosiglitazone, in colon cancer. Moser, a human colon cancer cell line, was treated with bexarotene and rosiglitazone alone or in combination and the effect on growth and differentiation were examined. The data demonstrated that the bexarotene/rosiglitazone combination produced greater efficacy in growth inhibition than either single agent. Furthermore, combination treatment acted cooperatively to decrease COX-2 expression and PGE2 synthesis while increasing expression of the differentiation marker, CEA. These findings were confirmed in vivo in a Moser xenograft tumor model. Collectively, our data suggest a potential role for utilizing a combination regimen of a RXR and PPARgamma agonist in the treatment of colon cancer.

Answer 8:

Bibliographic Information

A selective retinoid X receptor agonist bexarotene (LGD1069, Targretin) prevents and overcomes multidrug resistance in advanced prostate cancer.   Yen Wan-Ching; Lamph William W   Department of Molecular Oncology, Ligand Pharmaceuticals, Inc., San Diego, California 92121, USA. wyen@ligand.com   The Prostate (2006), 66(3), 305-16. Journal code: 8101368. ISSN:0270-4137. Journal; Article; (JOURNAL ARTICLE) written in English.   PubMed ID 16245282 AN 2006014288   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: We previously reported that a retinoid X receptor agonist bexarotene prevented and overcame acquired drug resistance in advanced breast cancer and non-small cell lung cancer. The present study was to evaluate the effect of bexarotene on the development of multidrug resistance in advanced prostate cancer. METHODS: Human prostate cancer cells PC3 were repeatedly treated in culture with paclitaxel, doxorubicin, or cisplatin with or without bexarotene for 3 months. Thereafter, cells were isolated and characterized for their drug sensitivity. RESULTS: Compared to parental cells, cells treated with a single therapeutic agent was resistant to the therapeutic agent, whereas cells treated with the combination remained chemosensitive. Cells with acquired drug resistance showed increased sensitivity to the cytotoxic agent when treated with the combination. Fluctuation analysis demonstrated that treatment with bexarotene decreased the rate of spontaneous development of drug resistance. These in vitro findings were further confirmed in the PC3 xenograft model. CONCLUSION: Our results suggest a role of bexarotene in combination with chemotherapeutic agents in prevention and overcoming acquired drug resistance in advanced prostate cancer. Copyright (c) 2005 Wiley-Liss, Inc.

Answer 9:

Bibliographic Information

The retinoid X receptor agonist bexarotene (Targretin) synergistically enhances the growth inhibitory activity of cytotoxic drugs in non-small cell lung cancer cells.   Hermann Thomas W; Yen Wan-Ching; Tooker Patricia; Fan Bingqi; Roegner Karen; Negro-Vilar Andres; Lamph William W; Bissonnette Reid P   Department of Molecular Oncology, Ligand Pharmaceuticals Inc., 10275 Science Center Drive, San Diego, CA 92121, USA   Lung cancer (Amsterdam, Netherlands) (2005), 50(1), 9-18. Journal code: 8800805. ISSN:0169-5002. Journal; Article; (JOURNAL ARTICLE) written in English.   PubMed ID 15993980 AN 2005494932   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

This study was designed to evaluate, using preclinical models of non-small cell lung cancer (NSCLC), the growth inhibitory effects of the retinoid X receptor (RXR) agonist bexarotene (LGD1069, Targretin) in combination with cytotoxic agents currently used as standard first-line therapy in advanced disease. Although single-agent bexarotene had modest growth inhibitory effects in several cell lines, efficacy was observed only in the micromolar range (>1muM), which approximates the plasma C(max) measured in pharmacokinetic studies in patients. However, when combined with paclitaxel or vinorelbine, bexarotene produced a concentration-dependent enhancement of the growth inhibitory activities of paclitaxel and vinorelbine. Formal synergy analysis using the Calu3 cell line demonstrated that the combination of bexarotene with either cytotoxic agent produced synergistic activity (combination index, CI<1). The in vitro observations were confirmed in vivo in a NSCLC xenograft tumor model (Calu3), where both bexarotene/paclitaxel and bexarotene/vinorelbine combinations produced significantly greater antitumor effects than the single agents. These results demonstrate that bexarotene can cooperate with widely used cytotoxic agents to decrease the growth of NSCLC tumor cells both in vitro and in vivo, and suggest the potential benefit of adding a RXR-selective agonist in combination with chemotherapy for NSCLC treatment. Furthermore, the data support the clinical observation from phase I/IIa trials suggesting that bexarotene has beneficial effects on survival when used in combination with cytotoxic agents in advanced NSCLC.

Answer 10:

Bibliographic Information

The selective retinoid X receptor agonist bexarotene (LGD1069, Targretin) prevents and overcomes multidrug resistance in advanced breast carcinoma.   Yen Wan-Ching; Lamph William W   Department of Molecular Oncology, Ligand Pharmaceuticals, Inc., 10275 Science Center Drive, San Diego, CA 92121, USA   Molecular cancer therapeutics (2005), 4(5), 824-34. Journal code: 101132535. ISSN:1535-7163. Journal; Article; (JOURNAL ARTICLE) written in English.   PubMed ID 15897247 AN 2005256809   MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Acquired drug resistance represents a major challenge in the therapeutic management of breast cancer patients. We reported previously that the retinoid X receptor-selective agonist bexarotene (LGD1069, Targretin) was efficacious in treating animal models of tamoxifen-resistant breast cancer. The goal of this study was to evaluate the effect of bexarotene on development of acquired drug resistance and its role in overcoming acquired drug resistance in advanced breast cancer. Paclitaxel, doxorubicin, and cisplatin were chosen as model compounds to determine the effect of bexarotene on the development of acquired drug resistance. Human breast cancer cells MDA-MB-231 were repeatedly treated in culture with a given therapeutic agent with or without bexarotene for 3 months. Thereafter, cells were isolated and characterized for their drug sensitivity. Compared with parental cells, cells treated with a single therapeutic agent became resistant to the therapeutic agent, whereas cells treated with the bexarotene combination remained chemosensitive. Cells with acquired drug resistance, when treated with the combination, showed increased sensitivity to the cytotoxic agent. Furthermore, cells treated with the combination regimen had reduced invasiveness and angiogenic potential than their resistant counterparts. These in vitro findings were further confirmed in an in vivo MDA-MB-231 xenograft model. Our results suggest a role for bexarotene in combination with chemotherapeutic agents in prevention

and overcoming acquired drug resistance in advanced breast carcinoma.

Answer 11:

Bibliographic Information

Abstract

Clinical studies have demonstrated that retinoids, including retinol (Vitamin A) and its synthetic derivatives, can eradicate leukoplakia and suppress the formation of squamous cell carcinoma of the head and neck (SCCHN). Nonselective retinoids have been shown to abrogate transcriptional activation of transforming growth factor-alpha (TGF-alpha) and epidermal growth factor receptor (EGFR), which characterize SCCHN. LGD1069 (Targretin) is a potent RXR-selective retinoic acid agonist with a reduced toxicity profile compared with other nonselective retinoids. We examined the effect of LGD1069 (10 microm) on cellular proliferation and expression of putative intermediate biomarker genes including TGF-alpha, EGFR, and RAR-beta in seven SCCHN cell lines. A quantitative reverse transcription-PCR assay using a novel "primer dropping" method was used to determine expression levels of EGFR, TGF-alpha, and RAR-beta before and after treatment with LGD1069 (10 microM). SCCHN proliferation was reduced by a mean of 50% at 4 days in seven SCCHN cell lines after LGD1069 treatment ($P <$ or $= 0.05$). EGFR expression levels were decreased by a mean of 58.4% ($P = 0.007$), TGF-alpha levels were decreased by a mean of 28.8% ($P = 0.01$), and RAR-beta levels were increased by a mean of 60% ($P = 0.03$). TGF-alpha stimulation of EGFR is associated with constitutive signal transducer and activator of transcription 3 (Stat3) activation in SCCHN. Abrogation of constitutive Stat3 activation was seen with LGD1069 treatment. These results suggest that an RXR-selective retinoic acid decreases SCCHN proliferation in part by interfering with TGF-alpha/EGFR autocrine signaling.